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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/700,971

11/04/2003

Muthiah Manoharan

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EXAMINER

MCGARRY, SEAN

ART UNIT

PAPER NUMBER

1635

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DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/700,971	Applicant(s) MANOHARAN ET AL.	
	Examiner Sean R. McGarry	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) ____ is/are pending in the application.
4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☐ Claim(s) ____ is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>1/18/05;4/07/05;8/16/05;11/06/06;2/26/08</u> . | 6) <input type="checkbox"/> Other: ____. |

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-103 and species "terminal position", "monomeric subunit", "steroid, and "cholesterol or cholesterol derivative" in the reply filed on 2/26/08 is acknowledged.

Claims 15, 18, 20, 26-35, 50, 53, 61-66, 68, 69, 77, 81, 89-94, and 96-98 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2/26/08. Applicant has canceled non-elected claims 104-109.

Priority

Claim 2 is granted an effective filing date of 7/09/03 as the first disclosure of "siRNA" is in provisional application 60/423,760.

Claims 38-49, 51, 52, 54-60, 67, 70-76, 78-80, 82, 84-88, 95 and 99-103 are granted an effective filing date of 7/09/03 as the first disclosure of "RISC", for example, is in application 10/616,241.

If applicant believes that the above claims are entitled to an earlier priority date applicant should point, with particularity, to support in the priority documents for the claimed invention.

Claim Rejections - 35 USC § 102

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The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 7-9, 22, 23, 24, 36 and 37 rejected under 35 U.S.C. 102(b) as being anticipated by Agrawal et al [WO94/01550, cited by applicant].

Agrawal et al have disclosed self stabilized oligonucleotides. It is disclosed that these oligonucleotides are double stranded and contain an antisense portion and a self stabilizing portion [sense]. At page 8 it is disclosed to added substituents including cholesteryl and other lipophilic groups. It is disclosed by Agrawal et al that the self-stabilized oligonucleotides can be DNA, RNA, or a combination thereof (see page 13, for example). It is disclosed at page 15, for example, that the self-complimentary region [sense] can be attached to the targeting region [antisense] via a non-nucleotide linker.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

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were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-14 16, 17, 19, 21-25, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al [above] in view of Manoharan et al [Tetrahedron Letters, Vol. 36(21):3651-3654, 1995 cited by applicant].

The invention is as clearly set forth in the claims.

Agrawal et al have disclosed self stabilized oligonucleotides. It is disclosed that these oligonucleotides are double stranded and contain an antisense portion and a self stabilizing portion [sense]. At page 8 it is disclosed to added substituents including cholesteryl and other lipophilic groups. It is disclosed by Agrawal et al that the self-stabilized oligonucleotides can be DNA, RNA, or a combination thereof. It is disclosed at page 15, for example, that the self-complimentary region [sense] can be attached to the targeting region [antisense] via a non-nucleotide linker. Agrawal et al have taught that the self-stabilizing region and the target region can be about 50 nucleotides or less (see pages 10 and 15, for example).

Agrawal et al do not specifically teach where a conjugate moiety is attached or teach cholesterol in particular, however, Manoharan et al have taught the use of Lipidic nucleic acids where it has been taught the use of moieties such as cholesterol linked to

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terminal ends, backbones or bases of antisense oligonucleotides where it is asserted as in Agrawal that these provide for more efficient antisense administration to cells.

One in the art would clearly combine the teachings of Agrawal and Manoharan et al to make the instant invention since Agrawal teaches the use of added substituents such as cholesteryl and Manoharan teaches the use of such substituents in more detail where both are directed to providing more effective antisense compounds. The determination of which strand or both strands to add a substituents is clearly a matter of optimization as the general use of substituents as claimed was established in the art at the time of invention.

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Claims 38-49, 51, 52, 54-60, 67, 70-76, 78-80, 82, 84-88, 95, and 99-103 rejected under 35 U.S.C. 103(a) as being unpatentable over Tuschl et al [US 2004/0259247] in view of Beach et al [US2002/0162126] and Manoharan et al[above].

The claimed invention is as clearly set forth in the claims.

Tuschl et al have taught the use of siRNA molecules for the inhibition of a desired target nucleic acid. It has been taught that the preferred length of these double stranded RNAs is 19-25 nucleotides. It has been taught at paragraph 15 and 179-181 what positions of an siRNA molecule are important for function and what areas are modifiable such as 5' and 3' ends. It has been taught to use siRNA in cell culture to

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determine gene function, for example (see paragraphs 28 and 29, for example). Tuschl et al do not specifically teach conjugate moieties.

Beach et al also teach the use of siRNA and teach that known methods in the art for introducing nucleic acids to cell may be used including lipid-mediated carrier transport (see paragraph 139, for example)

Manoharan et al have taught the use of Lipidic nucleic acids where it has been taught the use of moieties such as cholesterol linked to terminal ends, backbones or bases of antisense oligonucleotides where it is asserted as in Agrawal that these provide for more efficient antisense administration to cells. It has been taught that attachment at the 2' position of an oligonucleotide should minimize interference with hybridization.

One in the art would clearly combine the teachings of Tuschl, Beach and Manoharan et al to make the instant invention since Tuschl has taught the use of siRNA in cells and Beach has taught that lipid mediated or other known methods of nucleic acid delivery can be used with siRNA. Manoharan provide a teaching of how to make a use lipidic moieties to oligonucleotides and Tuschl et al have taught locations where siRNAs can be modified. The prior art teaches that the use of such conjugates was known in the art to enhance delivery of nucleic acid into cells, for example. The determination of which strand or both strands to add substituents would clearly have been a matter of optimization as the general use of substituents as claimed was established in the art at the time of invention and Tuschl has provided a clear basis for the locations of modification in an siRNA.

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R. McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sean R McGarry
Primary Examiner
Art Unit 1635

/Sean R McGarry/
Primary Examiner, Art Unit 1635

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